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(54) Title: METHOD OF TREATING ANGINA AND/OR ANGINAL EQUIVALENTS, AND PHARMACEUTICAL COMPOSITIONS AND KIT RELATED THERETO

(57) **Abstract**

The present invention provides a method of treating angina, e.g. stable angina, unstable angina and variant angina, and/or an anginal equivalent comprising administering a therapeutically effective amount of a multiplicity of liposomes, and preferably, large liposomes comprised of phospholipids substantially free of sterol to a subject for a treatment period. The method also includes administering an effective amount of an anti–anginal drug other than the liposomes. The invention also provides a method of treating claudication comprising administering a therapeutically effective amount of liposomes. In yet another variant, the invention provides a method of perioperative and/or pre–operative conditioning of a subject comprising administering liposomes. Several other inventions are also described herein.

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METHOD OF TREATING ANGINA AND/OR ANGINAL EQUIVALENTS, AND PHARMACEUTICAL COMPOSITIONS AND KIT RELATED THERETO

Patent Application

TO ALL WHOM IT MAY CONCERN:

Be it known that we, Dennis I. Goldberg, a citizen of the United States, residing at 109 Bent Road, Sudbury, Massachusetts 01776, and Kevin Jon Williams, a citizen of the United States, residing at 425 Wister Road, Wynnewood, Pennsylvania 19096, have invented a new and useful "*METHOD OF TREATING ANGINA AND/OR ANGINAL EQUIVALENTS, AND PHARMACEUTICAL COMPOSITIONS AND KIT RELATED THERETO*" of which the following is a specification.

METHOD OF TREATING ANGINA AND/OR ANGINAL EQUIVALENTS, AND PHARMACEUTICAL COMPOSITIONS AND KIT RELATED THERETO

BACKGROUND OF THE INVENTION

Chest pain can result from many causes, e.g. gastric discomfort, pulmonary distress, pulmonary embolism, musculoskeletal pain, pnuemothorax, cardiac non-coronary conditions, and ischemic coronary syndromes. Ischemic coronary syndromes include stable angina, unstable angina, variant angina, anginal equivalents, myocardial infraction, and related functional impairments, such as arrythmias, low cardiac output, heart failure, infarct extension, infarct expansion, reperfusion injury, and coronary thrombosis.

Stable angina is angina that recurs in a regular and characteristic pattern. A person recognizes that he/she is having angina only after several episodes have occurred, and a pattern has evolved. There is a certain level of activity or stress that provokes the angina and the pattern generally changes slowly.

Unstable angina is angina that appears as a very severe episode or as frequently recurring bouts of angina. In unstable angina, an established pattern of angina may change sharply. That is, the angina may appear at rest or may be provoked by far less exercise than in the past.

Variant angina pectoris is also known as Prinzmetal's angina. It differs from typical angina in that it occurs almost exclusively when a person is at rest. Attacks can be very painful and usually occur between midnight and 8 a.m. Variant angina pectoris, like other forms of angina and anginal equivalents, can be associated with acute myocardial infarction,

severe cardiac arrhythmias, including ventricular tachycardia, fibrillation, and even sudden death. Variant angina is due to coronary artery spasms, which can occur in close proximity to an atherosclerotic obstruction. Many of the people with angina go through an acute active phase. Anginal and cardiac events may occur frequently for six months or more.

Angina pectoris is defined as chest pain or discomfort of cardiac origin that usually results from a temporary imbalance between myocardial oxygen supply and myocardial oxygen demand. The discomfort is often induced by exercise, emotion, eating, or cold weather. Pain is more likely to occur when the subject is outdoors, especially when the temperature is extremely high or low and when the patient is walking uphill against the wind. Angina commonly occurs when a subject has eaten a heavy meal or when the subject is excited, angry or tense.

The normal coronary circulation is dominated and controlled by the myocardial requirements for oxygen. This need is met by the heart's ability to vary coronary vascular resistance (and therefore blood flow) considerably while the myocardium extracts a high and relatively fixed percentage of oxygen (*Harrison's Principles of Internal Medicine*, 12th edition, 1991, Chap. 16). Normally, intramyocardial resistance arterioles demonstrate an immense capacity for dilation. With exercise and emotional stress, the changing oxygen needs affect coronary vascular resistance and in this manner regulate the supply of blood and oxygen (metabolic regulation). These same vessels adapt to physiologic alterations in blood pressure in order to maintain coronary blood flow at levels appropriate to myocardial needs (autoregulation). Although the large epicardial coronary arteries are capable of constriction and relaxation, in healthy persons they serve as conduits and are referred to as

"conductance vessels," while the intramyocardial arterioles normally exhibit striking changes in tone and are therefore referred to as "resistance vessels." *Id.*

Once severe stenosis of a proximal epicardial artery has reduced the cross-sectional area by more than approximately 70 percent, the distal resistance vessels will dilate to reduce vascular resistance and maintain coronary blood flow. A pressure gradient develops across the proximal stenosis, and poststenotic pressure falls. When the resistance vessels are maximally dilated, myocardial blood flow becomes dependent on the pressure in the coronary artery distal to the obstruction. In these circumstances, alterations in myocardial oxygenation can be caused by changes in myocardial oxygen demand and changes in the caliber of the stenosed coronary artery due to physiologic baso-motion, pathologic spasm, or small platelet plugs. All these transient events can upset the critical balance between oxygen supply and demand and thus presipitate myocardial ischemia.

The effects of ischemia are many. The inadequate oxygenation induced by coronary atherosclerosis may cause transient disturbances of the mechanical, biochemical, and electrical function of the myocardium. The abrupt development of ischemia usually affects a segment of left ventricular myocardium with almost instantaneous failure of normal muscle relaxation and contraction. The relatively poor perfusion of the subendocardium causes more intense ischemia of this portion of the wall. Ischemia of large segments of the ventricle will cause transient left ventricular failure, and if the papillary muscles are involved, mitral regurgitation can complicate this event. When ischemic events are transient, they may be associated with angina pectoris; if prolonged, they can lead to

myocardial necrosis and scarring with or without the clinical picture of acute myocardial infarction. See, *Harrison's Principles of Internal Medicine*, 12th edition, 1991 Chap. 189.

Underlying these mechanical distrubances are a wide range of abnormalities in cell metabolism, function, and structure. When oxygenated, the normal myocardium metabolizes fatty acids and glycose to carbon dioxide and water. With severe oxygen deprivation, fatty acids cannot be oxidized, and glucose is broken down to lactate; intracellular pH is reduced as are the myocardial stores of high-energy phosphates, adenosine triphosphate (ATP), and creatine phosphate. Impaired cell membrane function leads to potassium leakage and the uptake of sodium by myocytes. The severity and duration of the imbalance between myocardial oxygen supply and demand will determine whether the damage is reversible or whether it is permanent, with subsequent myocardial necrosis. *Harrison's Principles of Internal Medicine*, 12th edition, 1991.

Ischemia also causes characteristic electrocardiographic changes such as repolarization abnormalities, as evidenced by inversion of the T wave and later by displacement of the ST segment (*Harrison's Principles of Internal Medicine*, 12th edition, 1991, Chap. 176). Transient ST-segment depression often reflects subendocardial ischemia, while transient ST-segment elevation is though to be caused by more severe transmural ischemia. Another important consequence of myocardial ischemia is electrical instability, since this may lead to ventricular tachycardia or ventricular fibrillation (*Harrison's Principles of Internal Medicine*, 12th edition, 1991, Chap. 185). Most patients who die suddenly from ischemic heart disease do so as a result of ischemia-induced malignant

ventricular arrhythmias. (*Harrison's Principles of Internal Medicine*, 12th edition, 1991, Chap. 40).

It is an object of the present invention to solve the problems associated with the conventional therapies used to treat these various forms of angina, anginal equivalents and acute coronary syndromes.

SUMMARY OF THE INVENTION

The present invention provides a method of treating angina that includes administering a therapeutically effective amount of liposomes to a subject. Stable angina, unstable angina, variant angina and/or anginal equivalents are treated utilizing the method described herein. The liposomes are selected from the group consisting of large liposomes, small liposomes, and combinations thereof, and administered such that LDL levels in the subject do not substantially rise.

Where large liposomes are used, the large liposomes are chemical compositions of liposomes of a size, function, composition, or administration method or schedule so that the liposomes do not harmfully disbturb cholesterol homeostasis. Administering the liposomes includes slowly infusing the liposomes into a subject in one variant of the invention. In another variant of the invention, small doses of the liposomes are administered, separated in time, to avoid increasing the LDL concentration.

The method also includes periodically assaying the plasma LDL concentrations with an assay to obtain an assayed LDL concentration. The assay is selected from the group consisting of an assay of plasma esterified cholesterol, an assay of plasma apolipoprotein-B, a gel filtration assay of plasma, an ultracentrifugal assay of plasma, and a precipitation

assay having a component, the component selected from the group consisting of polyanions, divalent cations, and antibodies, an ultracentrifugal assay of plasma, a precipitation assay, a immuno-turbidimetric assay, and an electrophoretic assay to determine the level of a therapeutically effective amount of each of the liposomes.

The method uses therapeutically effective amounts of liposomes in the range of about 10 mg to about 1600 mg phospholipid per kg body weight per dose. The liposomes are given periodically during the treatment period in one embodiment, and are selected from the group consisting of uni-lamellar liposomes, pauci-lamellar, and multi-lamellar liposomes.

Preferably, the liposomes have diameters larger than about 50 nm, diameters larger than about 80 nm, and/or diameters larger than about 100 nm. The liposomes can also have diameters in the range of about 100 nm to about 150 nm, about 150 nm to about 200 nm, about 250 nm to 300 nm and/or about 300 nm to about 400 nm. Other preferred ranges of liposomes are described herein.

In another embodiment of the invention, the liposomes are given to a subject by intravenous bolus administration, intravenous infusion, and/or intra-peritoneal administration. Other routes are also contemplated, such as intramuscular, subcutaneous, intranasal, by inhalation, rectal, and by encapsulation into an orally or enterally absorbed form.

The method also includes a variant in which there is monitoring of a subject's cardiac function. A typical cardiac function that is monitored includes an EKG abnormality, an S-T segment change, an arrhythmia, an assessment of segmental wall

motion, blood viscosity, exercise tolerance, ambulatory EKG monitoring, and/or a cardiac wall motion abnormality.

In yet another variant of the invention, the method includes administering an effective amount of an anti-anginal drug other than the empty liposomes. "Empty" is standard terminology to indicate absence of an encapsulated drug within a liposome, or that no encapsulated drug is essential for one or more functions of the liposomes. The anti-anginal drugs include nitrates, beta blockers, calcium channel antagonists, coronary vasodilators, lipid lowering drugs, afterload reducing agents, inotropic agents, pre-load reducing agents and opiates.

A nitrate can include, by way of example, nitroglycerine, sublingually administered nitroglycerine, a long acting nitrate, an insublingual nitrate preparation, a buccal nitrate preparation, an oral nitrate preparation, a spray nitrate preparation, an oral nitroglycerin spray, an isosorbide dinitrate preparation, an isosorbide-5-Mononitrate preparation, a sustained-release preparation of isosorbide-5-mononitrate, a topical nitroglycerin, a nitroglycerin ointment, a nitroglycerin containing transdermal patch, and a silicone gel or polymer matrix impregnated with nitroglycerin.

A beta blocker can, by way of example, include a nonselective beta-blocking drug, propranolol, nadolol, penbutolol, pindolol, sotalol, timolol, carteolol, a drug that blocks both beta1 and beta2 receptors, a cardioselective beta blocker, acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and a drug that blocks a beta1 receptor while having a lesser effect on a beta2 receptor.

In one variant of the invention, a calcium channel antagonist is selected from the group consisting of a calcium antagonist, a compound that inhibits calcium ion movement through a slow channel in cardiac and smooth muscle membranes by noncompetitive blockade of a voltage-sensitive L-type calcium channel, a dihydropyridine, nifedipine™, a phenylalkylamine, verapamil™, a benzothiazepine, diltiazem™, nicardipine™, amlodipine™, and bepridil™, a second-generation calcium antagonist, nicardiopine™, isradipine™, amlodipine™, felodipine™ and a dihydropyridine derivative.

Yet other aspects of the invention involve administering an angiotensin-converting enzyme (ACE) inhibitor to the subject in combination with the liposomes, administering an anti-arrhythmic drug to the subject in combination with the liposomes, and/or effecting a positive life style change in the subject. Typical positive life style changes include weight loss, reduction of cigarette smoking, elimination of cigarette smoking, exercise, supervised exercise, reduced salt intake, reduced intake of saturated fatty acids, reduced intake of cholesterol, a reduction in total fat intake, avoidance of physical stress, avoidance of emotional stress, and reduced intake of calories.

Yet a further aspect of the invention includes, effecting an anti-anginal therapy in combination with the liposome administration. The anti-anginal therapy comprises treatment of a co-existing aggravating condition such as a treatment for hypertension, a treatment for hyperthyroidism, a treatment for pulmonary disease, a treatment for heart failure, and a treatment for anemia.

Another embodiment of the invention includes administering an anti-thrombotic therapy in combination with the empty liposome administration. Anti-thrombotic therapies

are selected from the group consisting of administering a therapeutically effective amount of an anti-platelet drug, administering a therapeutically effective amount of a drug that interferes with formation of a fibrin clot, and a thrombolytic therapy.

Another embodiment of the invention comprises a method of treating claudication comprising administering a therapeutically effective amount of liposomes. As above, the liposomes are selected from the group consisting of large liposomes, small liposomes, and combinations thereof, and the method can be combined with the other method steps described above and below.

Still another aspect of the invention includes a pharmaceutical kit for treating angina comprising: a first container having a liposome; and a second container having an anti-anginal drug other than the liposome.

The invention is also directed to a method of preoperative and/or perioperative conditioning of a subject comprising administering liposomes, alone or in combination with the administration of an anesthetic or sedative and/or a preoperative evaluation or perioperative evaluation of a subject's cardiac function.

The objects and features of the present invention, other than those specifically set forth above, will become apparent in the detailed description of the invention set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a side cross-sectional view of a lipoprotein and a liposome;

FIG. 2 illustrates a table of hepatic mRNA content (pg/μg) for CETP, HMG-CoAR, LDL receptors, and 7a-hydroxylase; and LDL ChE;

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/12962

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/127, 133

US CL : 424/450

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/450

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST: angina, liposomes, claudication

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95/23592 A (THE UNIVERSITY OF BRITISH COLUMBIA) 08 September 1995, abstract, examples and claims.	1-154
Y	US 5,843,474 A (WILLIAMS) 01 December 1998, abstract, col. 1, line 21 through col. 2, line 31, Examples and claims.	1-154
Y	US 5,674,488 A (REICH) 07 October 1997, abstact, col. 1, lines 57-59.	1-154
Y	US 4,895,719 A (RADHAKRISHNAN et al) 23 January 1990, abstract, col. 16, 31-43 and claims.	1-154

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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